

Remarks

I. Status of the Claims

Claims 89-126 are pending in the application, with claims 89, 91, 98-103, 105, 106, 108, 109, 117, 118 and 122-124 being the independent claims.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider the sole outstanding rejection and that it be withdrawn.

II. Rejection Under 35 USC § 112, First Paragraph

The Examiner has maintained the rejection of claims 89-126 under 35 USC § 112, first paragraph. *See* Paper No. 19, page 2. According to the Examiner,

the specification, while being enabling for culturing murine embryonic stem cell lines in a serum-free medium composition as set forth in the preferred embodiments of Tables 1-3 and Examples 1-5, and compositions composed thereof, does not reasonably provide enablement for culturing conditions or compositions for embryonic stem cells from other species.

Paper No. 19, pages 2-3 (emphasis in original). Applicants respectfully traverse the rejection.

The enablement requirement of 35 USC § 112, first paragraph, is satisfied if the claimed invention is enabled so that any person skilled in the art can make and use the invention without undue experimentation. *See In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). In order to establish a *prima facie* case of non-enablement the Examiner has the initial burden to set forth a reasonable basis to question the enablement

provided for the claimed invention. *See In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). To satisfy this burden, "it is incumbent upon the Patent Office . . . to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *See In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971) (emphasis in original). Applicants submit that the full scope of the claimed methods, compositions and products of manufacture could be practiced and made by those of ordinary skill in the art without undue experimentation. Additionally, Applicants maintain their position that the Examiner has not provided a sufficient explanation or sound scientific reasoning as to why the specification would not enable the claimed invention; therefore, the Examiner has not established a *prima facie* case of non-enablement.

The overall basis for the Examiner's rejection is his contention that the specification does not "reasonably provide enablement for culturing conditions or compositions for embryonic stem cells from other species [besides mouse]." *See* Paper No. 19, page 3. To support this conclusion, the Examiner has made four general assertions: (1) that the specification fails to provide evidence that totipotent embryonic stem cells capable of contributing to the germ line exist for any animal besides the mouse, *see* Paper No. 19, page 4; (2) that methods for isolating embryonic stem ("ES") cells and method for developing ES cell lines is "highly unpredictable," *see* Paper No. 19, page 5; (3) that conditions for culturing ES cells from one species may not be suitable for culturing ES cells from another species, *see* Paper No. 19, page 5; and (4) that there are "numerous permutations of conditions encompassed by the instant claims." *See* Paper No. 19, page 6. Each of these

assertions is addressed in turn below. Applicants submit at the outset that such assertions, taken alone or in combination with one another, fail to demonstrate that it would require undue experimentation for the skilled artisan to make and/or practice the subject matter encompassed by Applicants' claims. The Examiner therefore has failed to establish a *prima facie* case of non-enablement.

A. *The Existence of Totipotent Stem Cells from Species Other than Mouse*

The Examiner's first basis for the rejection is the assertion that the specification "fails to provide evidence that totipotent embryonic stem cell[s] capable of contributing to the germ line *exist* for any other animal besides the mouse." *See* Paper No. 19, page 4 (emphasis added).

As a preliminary matter, Applicants note that the term "embryonic stem cell," as used in the present application, is not limited in its definition to include only *totipotent* embryonic stem cells. The Examiner acknowledged that the term "embryonic stem cell" is defined in the specification as a cell which can give rise to many differentiated cell types in an embryo or an adult, including the germ cells (sperm and eggs). *See* Paper No. 19, page 4; *see also*, specification at page 14, lines 1-3. The Examiner then went on to state that "[t]he present art accepted supports this definition wherein an ES cell is a totipotent cell capable of contributing to all tissues of an animal including the germ cells (Nichols *et al.*, page 1341; first paragraph)." *See* Paper No. 19, page 4 (emphasis in original). Thus, the Examiner appears to have added to Applicants' definition of "embryonic stem cells" the requirement that the cells be totipotent. Applicants note, however, that there is nothing in Applicants' definition of "embryonic stem cell" that necessitates that the cells be totipotent. Moreover,

there is nothing in the scientific literature or in the knowledge possessed by persons having ordinary skill in the art that would indicate that the term "embryonic stem cell" necessarily means *totipotent* embryonic stem cell; that is, embryonic stem cells are often characterized as pluripotent¹. See, e.g., Du, F. *et al.*, *J. Reproduct. Fertil.* 104:219-223 (1995) (copy submitted as "Attachment 3" with the Reply filed on August 9, 2000) (*see* especially the first sentence of the *Introduction*, referring to "*Pluripotent* embryonic stem (ES) cells."); *see also* specification at page 14, lines 1-4.

Thus, the term "embryonic stem cell," as used in the present claims, is not limited to *totipotent* embryonic stem cells. Even if this were not the case, however, the rejection based on Applicants' alleged failure to demonstrate the existence of totipotent embryonic stem cells from species other than mouse would be improper. Applicants have previously shown that embryonic stem cells have been isolated from various animals besides mouse. See specification at page 18, line 28, through page 19, line 8; *see also* Applicants remarks presented in the Reply dated April 23, 2001 (Paper No. 9) at pages 7-10. The Examiner has stated that "none of the references [cited in Paper No. 9] provide substantive evidence that a totipotent ES cells exist other than for the mouse." See Paper No. 19, page 4 (emphasis in original). Applicants note that the absence of definitive evidence demonstrating that a particular embryonic stem cell is totipotent does not necessarily indicate that the cell is *not* totipotent. In order to establish a *prima facie* case of non-enablement, it is not sufficient for

¹Many types of pluripotent cells are known in the art. While several pluripotent cell lines have been demonstrated to be totipotent, many pluripotent cell lines have not yet been shown to be totipotent. Whether or not a pluripotent cell line is later demonstrated to be totipotent does not in any way detract from it being a pluripotent cell line. "Totipotent" is not Applicants' term and its presence in the Examiner's discussion only appears to cloud the issues of patentability.

the Examiner to point to the *lack* of positive evidence for enablement; the Examiner must provide specific evidence indicating that the invention is *not* enabled. *See Marzocchi*, 439 F.2d at 224, 169 USPQ at 370. Stated differently, the initial burden lies not with Applicants to provide evidence that the invention *is* enabled; the initial burden is on the Examiner to show that an invention is *not* enabled. *See Wright*, 999 F.2d at 1562, 27 USPQ2d at 1513.

B. The Level of Predictability Associated with Isolating ES Cells and Producing ES Cell Lines

As another basis for the rejection, the Examiner stated that "the art recognized that the methods for isolating ES cells is highly unpredictable." *See* Paper No. 19, page 5 (emphasis added). Applicants respectfully disagree with this assertion.

The Examiner has not provided sufficient evidence to demonstrate that the isolation of ES cells is "highly unpredictable." The Examiner has merely pointed to a particular reference (Cruz) that allegedly² states the obvious fact that there are differences in the early embryonic development of different animals. *See* Paper No. 19, page 5. The fact that there are differences in early embryonic development among different animals does not suggest, however, that the methods required for isolating ES cells from different animals is "highly

²In the Office Action (Paper No. 19), the Examiner has cited four references that have not previously been cited in the course of prosecution of this application by either Applicants or the Examiner. The references are "*Nichols et al.*," "*Cruz et al.*," "*Piedrahita et al.*," and "*Clark et al.*" The Examiner has not provided complete, identifying citations for these references. Applicants' undersigned representative alerted the Examiner to this omission in a telephonic conversation on May 29, 2002. The Examiner indicated that the references were inadvertently not included with the Office Action and that they would be mailed to Applicants' representative. The references in question, however, were never received. Applicants are therefore unable to verify the accuracy of the Examiner's remarks and conclusions regarding the teachings of these references.

unpredictable." The Examiner has also pointed to Piedrahita which supposedly indicates that "[c]onditions that allowed production of porcine ES-like cell lines did not allow development of ovine ES-like cell lines." *See* Paper No. 19, page 5 (citation omitted). Again, the fact that different conditions may be required to produce one species of ES-like cell lines as opposed to another does not indicate or suggest that the *process of ascertaining* such conditions would require undue experimentation or would be "highly unpredictable."

The Examiner further cited Cruz and Piedrahita for the proposition that "numerous attempts to isolate ES cells from species other than the mouse have been attempted however, demonstration that these cells are able to contribute to the germ line is awaited." Paper No. 19, page 5 (citation omitted). As discussed above, the Examiner has the initial burden of setting forth specific evidence indicating that the invention is non-enabled. *See Wright*, 999 F.2d at 1562, 27 USPQ2d at 1513. Therefore, negative inferences regarding enablement cannot be made simply because there is a *lack* of positive data. Thus, an *absence* of definitive evidence showing that ES cells from other species are able to contribute to the germ line, as asserted by the Examiner, does not indicate or suggest that non-mouse ES cells could not, under any circumstances, contribute to the germ line. That is, for cells that have not yet been positively shown to contribute to the germ line, persons of ordinary skill in the art would recognize that, under certain circumstances or conditions, such cells may in fact be capable of contributing to the germ line. In addition, there is no requirement in the art that every ES cell be able to contribute to the germ line. Finally, the Examiner's attention is drawn to the discussion set forth in Paper No. 9 at pages 7-10, wherein references describing the isolation of embryonic stem cells from several animals are discussed.

Accordingly, the Examiner has not provided any substantial evidence that would indicate to the skilled artisan that methods for isolating ES cells is "highly unpredictable."

C. *The Ability to "Extrapolate" From Conditions Shown to be Effective for Mouse ES Cells*

The Examiner has also asserted that, although the specification sets forth the conditions that are effective for the culturing of murine embryonic stem cells,

there is no indication that these conditions would be effective for [culturing embryonic stem cells from] any other animal, nor is there a nexus between the methods used to culture/isolate murine ES cells and there [sic: "their"] effectiveness for use in culturing/isolating ES cells from any other species. . . In view of the fact that the art recognizes that conditions for one ES cell may not be effective for the other ES cells it is maintained that the artisan would need specific and detailed guidance for each ES cell for each separate species, which the instant specification and the art of record fails to provide.

Paper No. 19, pages 5-6. Applicants respectfully disagree with these assertions.

To support the above-quoted assertions, the Examiner again has relied upon the supposed teachings of Piedrahita. Specifically, the Examiner stated that:

Piedrahita *et al.* teach that culturing and isolation conditions for one species may not be suitable for culturing and isolation of embryonic stem-like cells from another species. Therefore, it would be recognized by one of skill in the art that one cannot simply extrapolate from procedures shown effective in one species to use or develop procedures for another species.

Paper No. 19, page 5.

Even if, as the Examiner contends, the conditions that are effective for culturing embryonic stem cells from one species may not be suitable for culturing embryonic stem

cells from another species, this proposition does not support the conclusion that it would require *undue experimentation* to practice and/or make the subject matter encompassed by Applicants' claims. The Examiner has simply asserted that different conditions may be required for culturing ES cells from different species, not that it would require undue experimentation to identify and ascertain the specific conditions that are effective in the practice of the invention. In order to establish a *prima facie* case of non-enablement, it is not sufficient for the examiner to merely show that different conditions exist for practicing and/or making the subject matter encompassed by Applicants' claims; the Examiner must demonstrate that the process of ascertaining such conditions would require undue experimentation. *See Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The Examiner has not provided any such specific evidence or sound scientific reasoning as to why it would require undue experimentation to practice and/or make the full scope of Applicants' claimed invention and therefore has not established a *prima facie* case of non-enablement.

Additionally, the Examiner concluded that, since Piedrahita allegedly teaches that culture conditions for embryonic stem cell from one species may not be suitable for culturing embryonic stem cells from another species, "it would be recognized by one of skill in the art that one cannot simply *extrapolate* from procedures shown effective in one species to use or develop procedures for another species." *See Paper No. 19*, page 5 (emphasis added). Applicants respectfully submit that the Examiner's use of the term "extrapolate" is imprecise and does not provide any real explanation as to why the present invention would not be enabled. A skilled artisan would not simply "extrapolate" from the teachings set forth in the specification to determine the conditions necessary to practice and make the full scope of the invention. Rather, one of ordinary skill in the art would look to the specification and

the teachings in the art to deliberately, carefully and scientifically test a variety and range of parameters in order to identify the appropriate conditions. The necessity of some experimentation to practice a claimed invention does not render an invention non-enabled as long as the quantity of experimentation needed is not regarded as undue. *See In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). The patent law does not require, in order to satisfy the enablement requirement of § 112, first paragraph, that a skilled artisan be able to "extrapolate" from the teachings of the specification to be able to practice the claimed invention. "The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *United States v. Teletronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988).

Contrary to the Examiner's contention that culture conditions for ES cells of one species may not be suitable for culturing ES cells from another species, Applicants point out that there are several examples in the scientific literature showing that media and conditions that have been shown to be effective for mouse ES cells are also suitable for culturing and maintaining human and primate ES cells. These results directly contradict the major premise upon which the enablement rejection is based.

One example demonstrating that human ES cells have been cultured in the same type of serum-free medium as is typically used for culturing mouse ES cells is Amit, M. *et al.*, *Developmental Biol.* 227: 271-278 (2000) (Attachment A). According to the "Materials and Methods" section, *see* Amit at page 272, bottom left column:

[c]ulture medium for the present work consisted of 80% KnockOut Dulbecco's modified Eagle's medium, *an optimized medium for mouse ES cells* (Gibco BRL,

Rockville, MD), 1mM L-glutamine, 0.1 mM β -mercaptoethanol, and 1% nonessential amino acids stock (Gibco, BRL), supplemented with either 20% fetal bovine serum (HyClone, Logan UT) or 20% *KnockOut SR, a serum replacer optimized for mouse ES cells* (Gibco BRL). (Emphasis added).

Other examples in which serum-free culture medium typically used for culturing mouse ES cells was used to culture human ES cells include the following: Assady, S. *et al.*, *Diabetes* 50:1691-1697 (2001) (Attachment B), *see* especially page 1692, top left column; Xu, C. *et al.*, *Nature Biotech.* 19:971-974 (2001) (Attachment C), *see* especially page 973, right column; Kaufman, D.S. *et al.*, *Proc. Natl. Acad. Sci. USA* 98:10716-10721 (Attachment D), *see* especially paragraph bridging pages 10716-10717; Lebkowski, J.S. *et al.*, *Cancer J.* 7 (Suppl. 2):S83-S93 (2001) (Attachment E), *see* especially page S84, left column; Schuldiner, M. *et al.*, *Proc. Natl. Acad. Sci. USA* 97:11307-11312 (2000) (Attachment F), *see* especially page 11307, right column; and Tzukerman, M. *et al.*, *Mol. Biol. Cell* 11:4381-4391 (2000) (Attachment G), *see* especially page 4384, right column. Assady, S. *et al.* also note that "[m]ethods for the induction of differentiation in mouse ES cells were applied herein for the induction of hES [human embryonic stem cell] differentiation." *See* Assady at page 1692, left column (citations omitted).

Serum-free medium that has been shown to be effective for culturing mouse ES cells has additionally been shown to be useful in maintaining undifferentiated primate ES cells. *See, e.g.*, Kawasaki, H. *et al.*, *Proc. Natl. Acad. Sci. USA* 99:1580-1585 (2002) (Attachment H).

As mentioned above, the rejection for lack of enablement is based, to a large extent, on the contention that "conditions for one ES cell may not be effective for the other ES cells.

.. " Paper No. 19, page 6. The above-described references directly refute this contention.

D. The Inclusion of "Numerous Permutations of Conditions" Within Applicants' Claims

The Examiner has also made reference to the mathematical formula set forth in the Advisory Action dated August 14, 2001 (Paper No. 13). According to the Examiner:

The mathematical formulation set forth previously in the advisor [sic] action provides for the numerous permutations of conditions encompassed by the instant claims, and in view of the unpredictability of the art, there is no reasonable expectation that any of the conditions would be effective in culturing ES cells. Examiner would agree that the amount of experimentation is alone not sufficient to establish a *prima facie* case, however in the instant circumstance, due to the lack of predictability in the art for ES cells, the large breadth of conditions taught by the instant specification and encompassed by the claims represents an undue amount of experimentation with no reasonable expectation of success³.

Paper No. 19, page 6.

Thus, the Examiner's conclusion regarding the amount of experimentation needed to make and practice the claimed invention is based on two factors: (a) the large number of medium formulations that could possibly be made in view of the teachings of the specification (as illustrated by the formula described in Paper No. 13), and (b) the alleged "lack of predictability in the art for ES cells." The combination of these two factors,

³The Examiner, in referring to "reasonable expectation of success," appears to be confusing concepts associated with an obviousness rejection under § 103 with the legal standard for enablement under § 112, first paragraph. The legal standard for enablement is that the claimed invention must be enabled so that any person skilled in the art can make and use the invention without *undue experimentation*. See *Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. There is no requirement that there be a "reasonable expectation of success" to satisfy the enablement requirement.

according to the Examiner, indicates that it would require undue experimentation to practice the claimed invention. Applicants respectfully disagree with the validity and significance of both of the factors upon which the Examiner has based this conclusion.

First, even though there may be multiple medium formulations that are encompassed by, or that are capable of being used with, the compositions and methods of Applicants' claims, the Examiner has not demonstrated that it would require more than routine experimentation for the skilled artisan to ascertain which formulations are most effective. Applicants submit that a skilled artisan would be able to determine which, among the possible formulations, would be most appropriate in any particular context.

Second, the simple fact that multiple formulations could possibly be made does not indicate that a person of ordinary skill in the art would need to make and test each and every one of them in order to find appropriate conditions for the practice of the claimed invention. The skilled artisan, in light of the teachings available in the art, would know which combinations would most likely be useful in the context of the present invention. Indeed, Applicants assert that a skilled artisan, based simply on the present specification and on the common general knowledge available in the art, would be able to immediately set aside the vast majority of possible combinations that are less likely to be effective. Thus, among the large number of possible formulations, the skilled artisan would be able to easily identify those that are most likely to be appropriate for use in the context of the present invention.

Third, with respect to the alleged "lack of predictability in the art for ES cells," Applicants note that the Examiner has not set forth acceptable evidence or sound scientific reasoning that would indicate that the particular aspects of embryonic stem cells that are

relevant to the practice and making of the present invention are, in fact, unpredictable. *See* Applicants' discussion under sections *II.B* and *II.C*, *supra*.

E. Summary

The Examiner has not satisfied his burden in demonstrating that it would require undue experimentation to practice and/or make the claimed invention based on the teachings of the specification and the knowledge generally available to those skilled in the art. Accordingly, Applicants respectfully assert that the rejection under 35 USC § 112, first paragraph, is improper and should be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Frank R. Cottingham
Attorney for Applicants
Registration No. 50,437

Date: 6/12/02

1100 New York Avenue, N.W.
Suite 600
Washington, D.C. 20005-3934
(202) 371-2600